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Neural Modulation of the Immune Response through the Benzodiazepine/GABA Receptor Chloride Ionophore Complex.

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Prince K. Arora, Ph.D.,

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This project examines the role of the benzodiazepine/GABA receptor chloride ionophore complex (Supramolecular Complex) in the control of immune functions. We have found that the suppression of allogeneic CTL response by the benzodiazepine receptor inverse agonist, FG 7142 is dose-dependent, and that this suppression is long lasting. FG 7142 suppressed CTL response in male mice only, suggesting that the FG 7142-induced immune suppression may be sexually dimorphic. Natural Killer (NK) cell activity was also suppressed 2 hr after administration of FG 7142 and was still manifest 24 hr later. A profound suppression of immune functions (CTL, NK, and MLR responses) was also observed 2 hr after administration of a single dose of Alprazolam (a triazolbenzodiazepine with high affinty for "central" but not "peripheral" benzodiazepine receptors). These results suggest that the benzodiazepine receptors and the pathways subserved by these receptors may be important in the neural control of immunity. Keywords: immunochemistry

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Prince K. Arora and Phil Skolnick, Laboratory of Neuroscience, NIDDK, National Institutes of Health, Bethesda, MD 20892

I. INTRODUCTION

During the past two decades, it has been shown that the immune system can be modulated not only by "classical" means (Jerne, 1955; Jerne, 1974; Benacerraf and McDevitt, 1972; Gershon, 1974; McDevitt, 1980) but also through mechanisms controlled by the central nervous system (CNS) (Solomon, 1969; Besedovsky and Sorkin, 1977). For example, both psychosocial and environmental stressors have been shown to affect the humoral and cellular components of immunity in laboratory animals and man (Ader, 1981; Tekoma and Huey, 1985; Arora et al, 1987). Individuals with psychosis (Kovaleva et al, 1977), bereavement and depression (Barthrop et al, 1977), and emotional stress exhibit impaired immune reactivity (Solomon, 1969), and investigations of experimental animals subjected to stress by overcrowding or avoidance conditioning have shown impaired immune responsiveness (Rassmussen et al, 1959; Solomon, 1969).

Our laboratory has had a longstanding interest in the neurochemical bases of anxiety (Tallman et al, 1980; Skolnick and Paul, 1983). Pharmacological, biochemical and behavioral evidence suggests that the benzodiazepine/GABA receptor chloride ionophore complex ("supramolecular complex") mediates the anti-anxiety effects of benzodiazepines, barbiturates, and other pharmacologically important agents (Usdon et al, 1982). Several lines of evidence suggest that the supramolecular complex is involved in the physiological control of stress and anxiety (Ninan et al, 1982; Havoundjian et al, 1987). Since the role of the "supramolecular complex" in the neural modulation of immunity had not been investigated, we initiated such studies. Thus, we recently found that the administration of the benzodiazepine receptor (BzR) "inverse agonists" FG 7142 (N-methyl-ß-carboline-3-carboxamide) and DMCM (3-carbomethoxy-4-ethyl-6,7-dimethoxy-ß-carboline) produced a profound suppression of T-cell functions in mice (Arora et al, 1987). Since ß-carbolines like FG 7142 have been demonstrated to produce a BzR-mediated behavioral, somatic, and endocrine syndrome reminiscent of stress or anxiety in rodents and primates, including man (Ninan et al, 1982; Dorow et al, 1983; Insel et al, 1984), our findings (Arora et al, 1987) suggest that the benzodiazepine receptors in the CNS and the pathways subserved by these receptors may be important in the neural control of immunity.

II. PROGRESS REPORT

A. IMMUNOMODULATION THROUGH THE BENZODIAZEPINE/GABA RECEPTOR CHLORIDE IONOPHORE COMPLEX (SUPRAMOLECULAR COMPLEX) IN THE CNS:

1. Cytotoxic T-lymphocyte (CTL) Response Studies:

a). Dose-Kinetics of FG 7142-Induced Immunosuppression: The immunoregulatory effects of FG 7142 were studied in vivo by administering varying doses of FG 7142 to groups of NFR/N mice (Small Animal Section, NIH, Behtesda, MD). FG 7142 (12.5-100 mg/kg, i.p.) was injected in 0.15 ml of vehicle (20% Emulphor). The placebo group received an equal volume of vehicle. Spleens were removed 24 hr later and the CTL response measured as described (Arora and Shearer, 1981). Results presented in Fig. 1 indicate that these doses of Fg 7142 significantly suppressed the CTL response. Furthermore as the dose of Fg 7142 was increased, greater suppression of the CTL response resulted, with 25 mg/kg being the optimal dose. These results suggested that the suppression of the CTL response by FG 7142 is dose-dependent.

b). FG-7142-Induced Immunosuppression is long-lasting: In preliminary studies, we had shown that 24 h after administration of these ß-carbolines, both mitogen stimulated T-cell proliferation and allogeneic CTL response were suppressed (Arora et al, 1987). The length and magnitude of suppression are unknown. Animals were administered with 25 mg/kg of FG 7142, and at different time periods, animals were sacrificed and the CTL response measured as described (Arora and Shearer, 1981). Suppression of the CTL response was manifest even after 24 days suggesting that the suppression of the CTL response by FG 7142 is very long lived (Fig. 2). It would be of interest to extend this time course study to determine how long this suppression by FG 7142 lasts.

c). Influence of Gender on Stress-induced Immunosuppression: Both male and female NFR/N mice were administered with FG 7142 (25 mg/kg) and 24 h later animals were sacrificed and the allogeneic CTL response measured. The placebo animals received vehicle only. Results as shown in Fig. 3 indicate that FG 7142 suppressed allogeneic CTL response in male mice only. Administration of doses even several-fold higher (100 mg/kg) failed to produce a similar effect in female mice. These results suggest that FG 7142-induced immunosuppression may be sexually dimorphic. It would be of interest to investigate the mechanisms through which females appear resistant to stress-induced immunosuppression. Such studies would include an examination of the dose-effect relationship, duration of immunosuppression, and determination of suppression on specific T-cell populations in both sexes.

2. Natural Killer (NK) Cell Activity Studies:

During the first year, we also investigated whether the supramolecular complex modulates another immune parameter, NK

cell activity. Male B10.BR mice (Jackson Laboratories, Bar Harbor, ME) were injected with FG 7142 (5-50 mg/kg) or an equal volume of vehicle. Spleens were removed 2 and 24 hr later and NK cell activity measured using chromium-51 (^{51}Cr) release assay as described (Arora and Shearer, 1981; Petitto et al, 1988). A dose-dependent supression of NK cell activity was observed both at 2 hr (Fig. 4A) and 24 hr (Fig. 4B) after administration of FG 7142. A similar dose-dependent suppression of NK cell activity was observed at other effector:target (E:T) cell ratios (100:1 and 25:1) (data not shown). The doses of FG 7142 needed to suppress NK cell activity (Petitto et al, 1988) were consistent with those that produce both behavioral and endocrine changes in rodents reminiscent of stress or anxiety (File and Pellow, 1985; Stephens and Kehr, 1985) and those that suppressed T-cell functions (Arora et al, 1987). Pretreatment of mice with a specific, high affinity BzR antagonist Ro 15-1788 (10 mg/kg) 15 min prior to administration of FG 7142 (25 mg/kg) resulted in a significant reduction of this suppression (Fig. 5). In this series of experiments, FG 7142 suppressed NK cell activity by 35.6% (compared with vehicle treated animals) which was reduced to 16.6% in mice pretreated with Ro 15-1788 (Fig. 5). Ro 15-1788 did not reduce NK cell activity when administered alone (Fig. 5).

Several observations in this study suggest that the suppression of NK cell activity by FG 7142 is mediated via occupation of BzR in the CNS. Direct addition of FG 7142 (1 μM-10 μM) to the ^{51}Cr release assays during a four hr incubation period had no effect on NK cell activity (data not shown). Furthermore, neither Ro 15-1788 nor inverse agonist FG 7142 bind with high affinity to peripheral benzodiazepine receptors (pBzR) (Marangos et al, 1982; Schoemaker et al, 1983) that are present on cells of the immune system (Zavala et al, 1985; Ruff et al, 1985; Moingeon et al, 1985; Zavala and Lenfant, 1987). Finally, the antagonism of FG 7142-induced suppression of NK cell activity by Ro 15-1788 is consistent with the ability of this compound to block the effects of both BzR agonists (i.e. substances with benzodiazepine-like qualities) and inverse agonists (Skolnick and Paul, 1983). These findings suggests that the BzR inverse agonists may be useful tools to study neural-immune interactions, and support the hypothesis (Arora et al, 1987) that the pathways subserved by the "supramolecular complex" may play an important role in the neural modulation of immunity.

Recent studies have demonstrated that the Long-Sleep (LS) and Short-Sleep (SS) mouse lines, bidirectionallly selected for their hypnotic sensitivities to a single dose of ethanol, are also differentially sensitive to other depressants such as barbiturates (McIntyre and Alpern, 1985, 1986; Marley et al, 1986) and benzodiazepines (McIntyre and Alpern, 1986), as well as convulsants such as 3-carbomethoxy-ß-carboline, picrotoxin, and bicuculline (Philips and Dudek, 1983; McIntyre and Alpern, 1986). Thus, LS and SS mouse lines represent a unique genetic model which can be utilized to assess the role of the supramolecular complex in the neural modulation of immune functions. Since the

well-described difference in drug sensitivities of these lines appears to be mediated through inherent differences in biochemical and biophysical properties of the supramolecular complex (Marley and Wehner, 1986; McIntyre et al, 1988), the assessment of NK cell function could be accomplished without confounding pharmacological intervention. Spleen cells from male LS and SS mice (Institute for Behavioral Genetics, University of Colorado, Boulder, CO), were tested for NK cell activity by using a ^{51}Cr release assay as described (Arora and Shearer, 1981; Petitto et al, 1988). NK cytotoxic activity ranged from 6.0-16.9% in the LS mice and 3.6-7.0% in SS mice, respectively (Fig. 6). The NK cell activity of the LS line was higher than the SS line at each E:T ratio tested, with differences ranging from 67-142%. [Significant differences in the total numbers of cells per spleen were also observed between these lines. The number of viable cell per spleen was 68% higher in the LS line ($178.8 \pm 15.3 \times 10^6$) than in the SS line ($106.3 \pm 6.5 \times 10^6$) ($p<.001$, Student's t-test)]. Since NK cell activity is assayed with equal number of effector spleen cells from each line, the greater number of splenic leukocytes in LS mice, thus, greatly enhanced the genetic differences in NK cell activity between LS and SS. In total, these observations, in concert with the findings that benzodiazepine ligands affect immune functions (Arora et al, 1987), provide additional support for the hypothesis that the "supramolecular complex" (in the CNS) regulates NK cell activity.

3). Effect of Alprazolam on Selected Aspects of Immunity:

Previous studies have demonstrated that anxiolytic benzodiazepines can modulate immune function (Descotes et al, 1982; Okimura & Nagata 1986; Pericic et al, 1987; Zavala & Lenfant 1987). These effects have generally been attributed to modulation of "peripheral" rather than "central" benzodiazepine receptors (Zavala & Lenfant 1987). "Peripheral" benzodiazepine receptors have been identified on components of the immune system such as macrophages (Zavala & Lenfant 1987) and human monocytes (Ruff et al. 1985). In order to determine whether immune modulation by benzodiazepine receptor agonists is mediated via "central" benzodiazepine (i.e. the benzodiazepine/GABA receptor chloride channel complex), we examined in this study the effects of alprazolam (a triazolobenzodiazepine with high affinity for "central" but not "peripheral" benzodiazepine receptors) on selected aspects of cellular immunity.

A single dose of alprazolam (0.5 or 1.0 mg/kg, i.p.) was administered to male B10.BR mice. At different time intervals (2, 2.5 or 24 hr later), selected aspects of immune function were examined. A profound suppression of immune function was observed two hr after injection. This suppression was manifest as a decrease in mitogen-stimulated T and B lymphocyte proliferation. A significant reduction in mixed leucocyte reaction (MLR) and allogeneic cytotoxic T lymphocyte (CTL) response was also observed upon administration of alprazolam. However, the immunosuppression produced under these conditions appeared short

lived. At 2.5 hr, only the CTL and MLR responses were suppressed whereas 24 hr after the initial dose of alprazolam, none of the parameters were different from those measures in vehicle treated mice (Table I).

These data suggest that benzodiazepine anxiolytic drugs may have significant though short-lived effects on immune function through activation of "central" receptors, since alprazolam has high affinity for "central" benzodiazepine receptors but very low affinity for the "peripheral" receptors. However, in order to assess the implication of these data for clinical use of antianxiety agents in the human population, we will have to delineate further the dose range (0.05-5.0 mg/kg) and time course of the immunosuppressive effects of alprazolam.

Arora et al (1987) have recently reported a profound inhibition of immune function after administration of the anxiogenic ß-carbolines FG 7142 and DMCM. These anxiogenic drugs act as antagonists to benzodiazepines at the benzodiazepine/GABA receptor chloride channel complex (Bruun-Meyer 1987). Hence in future experiments we will study a possible interactive effect between such anxiogenic agents and alprazolam. By carefully examining the time interval required to see an interactive effect between administration of the ß-carbolines and alprazolam, we will be able to relate activation of the receptor complex to the effects on the immune system.

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IV. PUBLICATIONS (Year 1):

Manuscripts:

1. Arora, P.K.: (1988). Neuromodulation of Natural Killer (NK) Cells. In "Neuroimmunomodulation" (Ed. Edward J. Goetzl) Alan R. Liss, Inc. (submitted)

2. Petitto, J.M., Skolnick, P., and Arora, P.K.: (1988). Suppression of Natural Killer (NK) Cell Activity by FG 7142, A Benzodiazepine Receptor "Inverse Agonist". Brain Behavior and Immunity (submitted)

3. Petitto, J.M., McIntire, T.D., Skolnick, P., and Arora, P.K.: (1988). Natural Killer (NK) Cell Activity in the Long-Sleep (LS) and Short-Sleep (SS) Mouse Lines: A Possible Association Between Alcohal Sensitivity and Cellular Immunity. J. Neuroimmunology. (submitted)

4. Arora, P.K., Fride, E., Petitto, J., Waggie, K., and Skolnick.: (1988). Are Morphine-Induced Alterations in Immune Function a Predisposing Factor for AIDS. Nature (to be submitted)

5. Ostrowski, N., Kress, D.W., Hagan, A., and Arora, P.K. (1988). Sexual Behavior Suppresses Immune Function. Nature (submitted)

6. Ostrowski, N., Kress, D.W., Hagan, A., and Arora, P.K. (1988). Sexual Behavior Suppresses Antibody Production in the Golden Hamster (Mesocricetus auratus). Brain, Behavior and Immunity (submitted)

7. Kress, D.W., Ostrowski, N.L., and Arora, P.K.: (1988). Mating Suppresses Splenic Natural Killer (NK) Cell Cytotoxicity in Male Golden Hamsters Brain, Behavior and Immunity. (submitted)

Abstracts:

1. Petitto, J.M., Skolnick., and Arora, P.K.: (1988). Suppression of Natural Killer Cell Activity by FG 7142, A Benzodiazepine Receptor "Inverse Agonist". FASEB Summer Research Conference on "Neuroimmunomodulation". Copper Mountain, Colorado.

2. Fride, E., Skolnick, P., and Arora, P.K.: (1988). Transient Immunosuppressive Effects of Alprazolam in Mice. FASEB Summer Research Conference on "Neuroimmunomodulation". Copper Mountain, Colorado.

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TRAINING ACTIVITIES : Two post-docs (Ester Fride, Ph.D., and John Petitto, M.D.) and two summer students (Douglas Kress and Bradford McRae) have been trained during the first year of the project.

AWARDS AND FELLOWSHIPS:

1). Mentor, NIH Summer Student Fellowship to Dr. Arora.

2). Mentor, The Armenian Assembly Summer Intern Program. Armenian Assembly of America, Washington, D.C.

3). International Travel Award to Dr. Arora to attend IV International Conference on AIDS, Stockholm, Sweden, 1988.

Figure. 1

DOSE-KINETICS OF FG 7142-INDUCED SUPPRESSION ON THE CTL RESPONSE

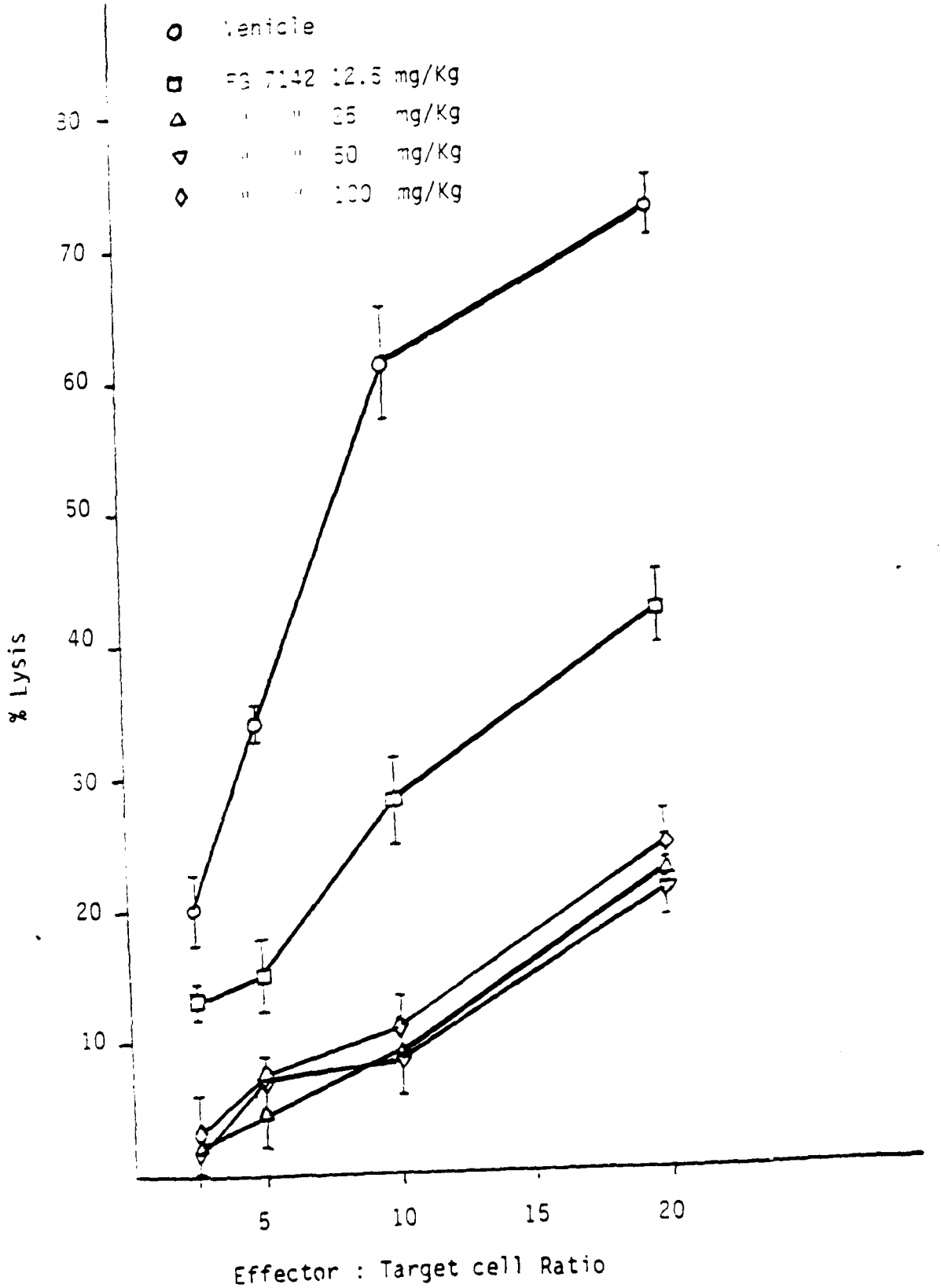


Figure. 2

TIME-KINETICS OF FG 7142-INDUCED SUPPRESSION ON THE CTL RESPONSE

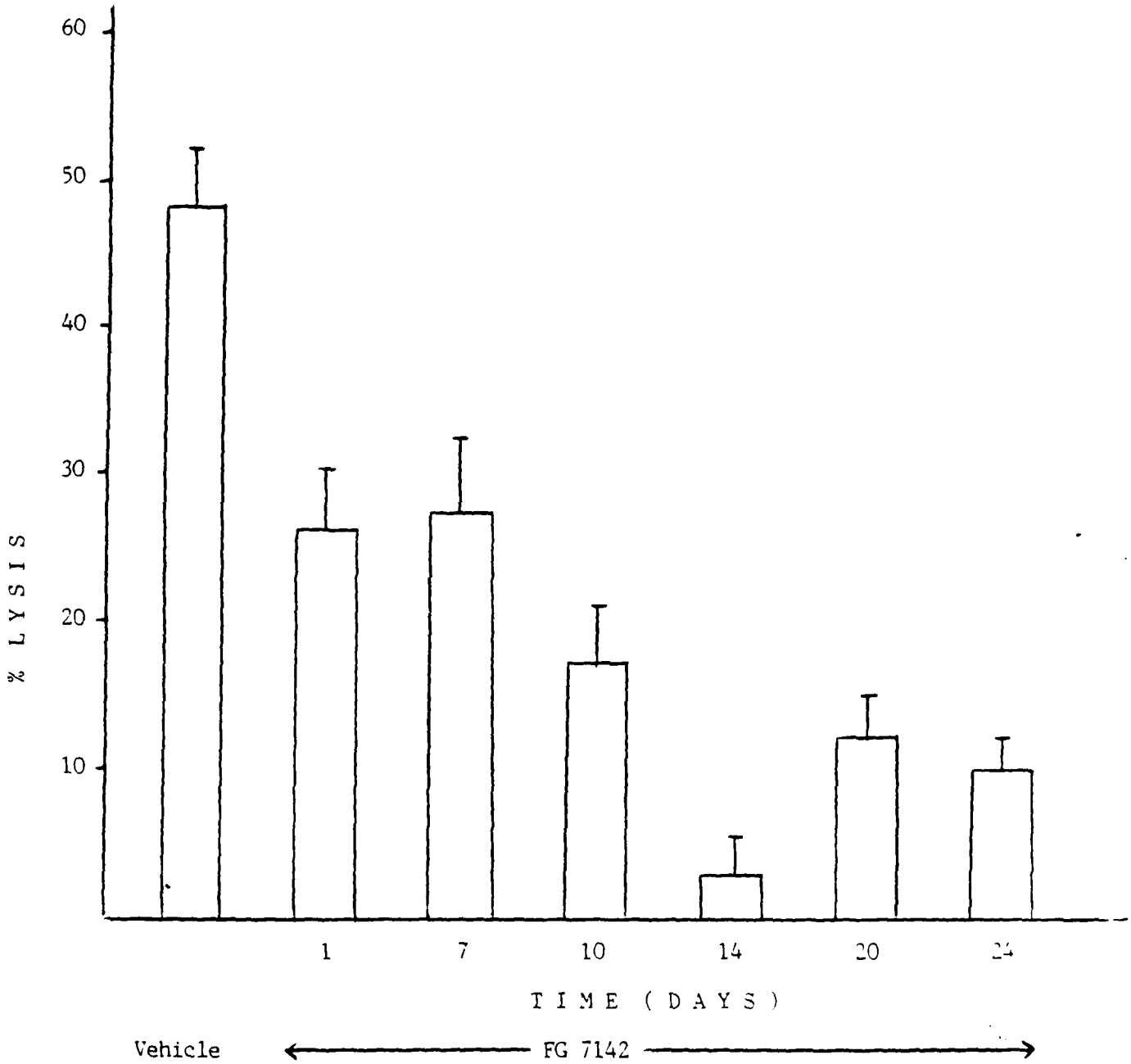


Figure. 3

EFFECT OF FG 7142 ON THE CTL RESPONSE OF FEMALE AND MALE MICE

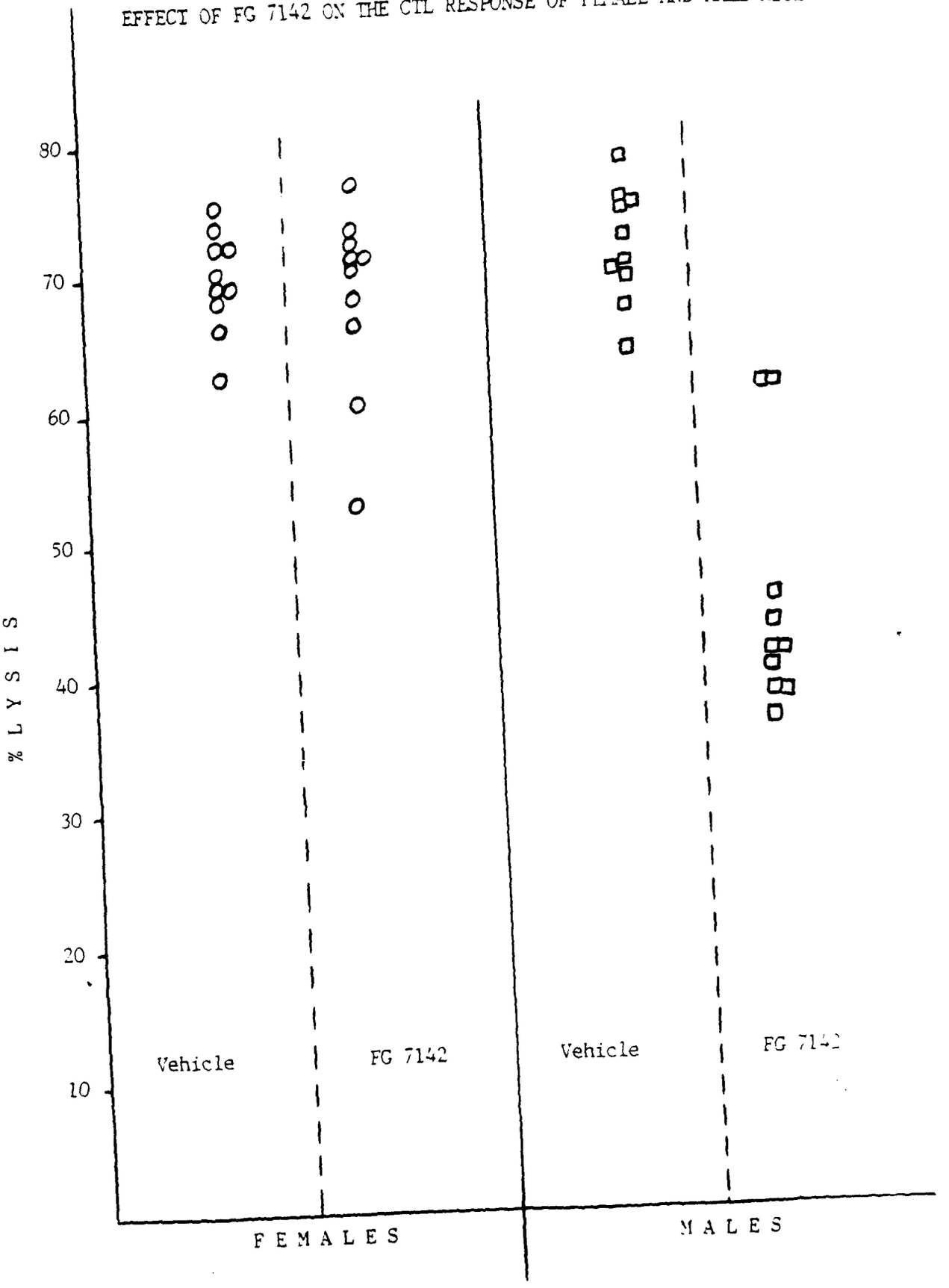
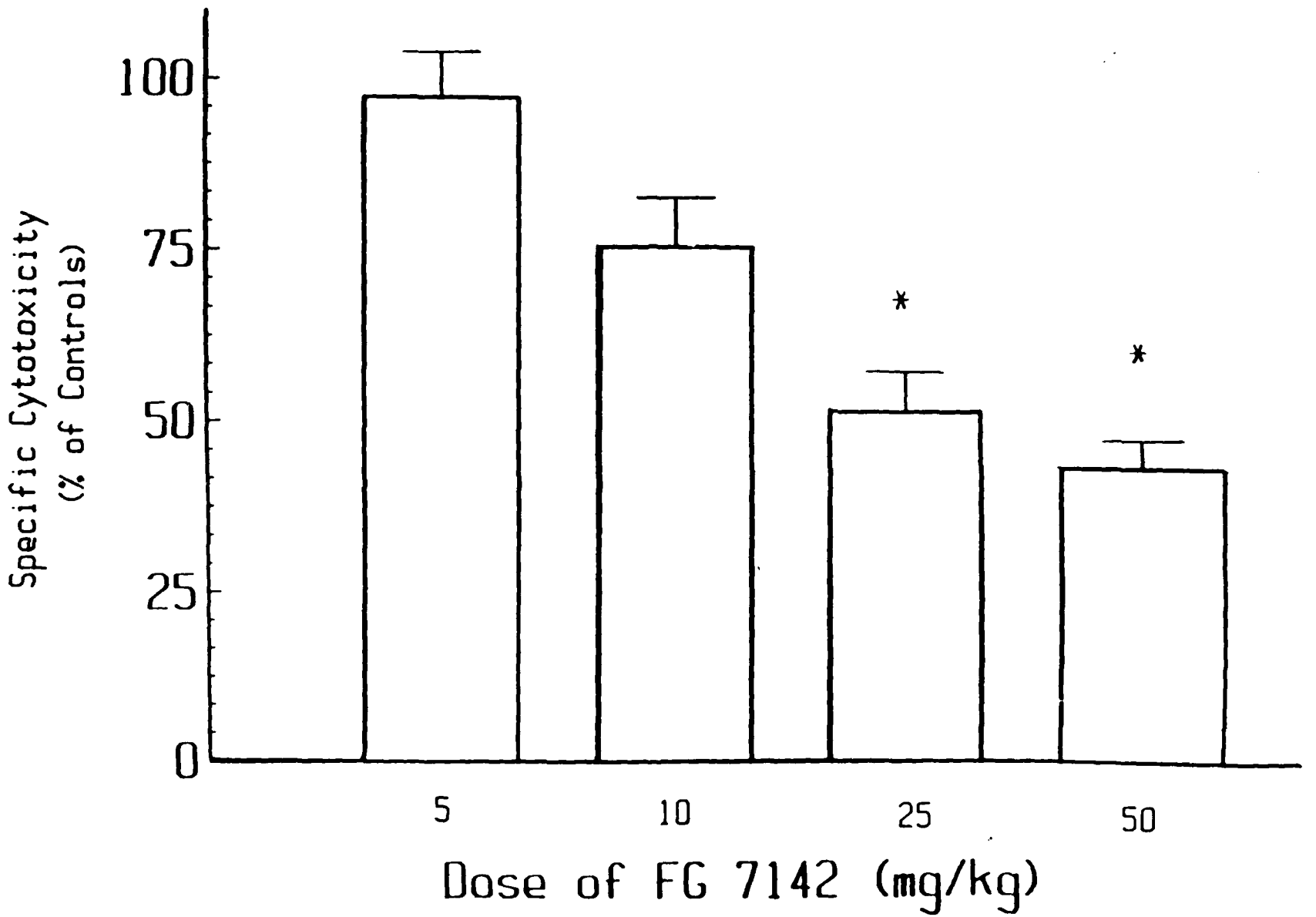


Figure. 4 A


Specific Cytotoxicity
(% of Controls)
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75
50
25
0
*
*
5
10
25
50
Dose of FG 7142 (mg/kg)

Figure. 4 B

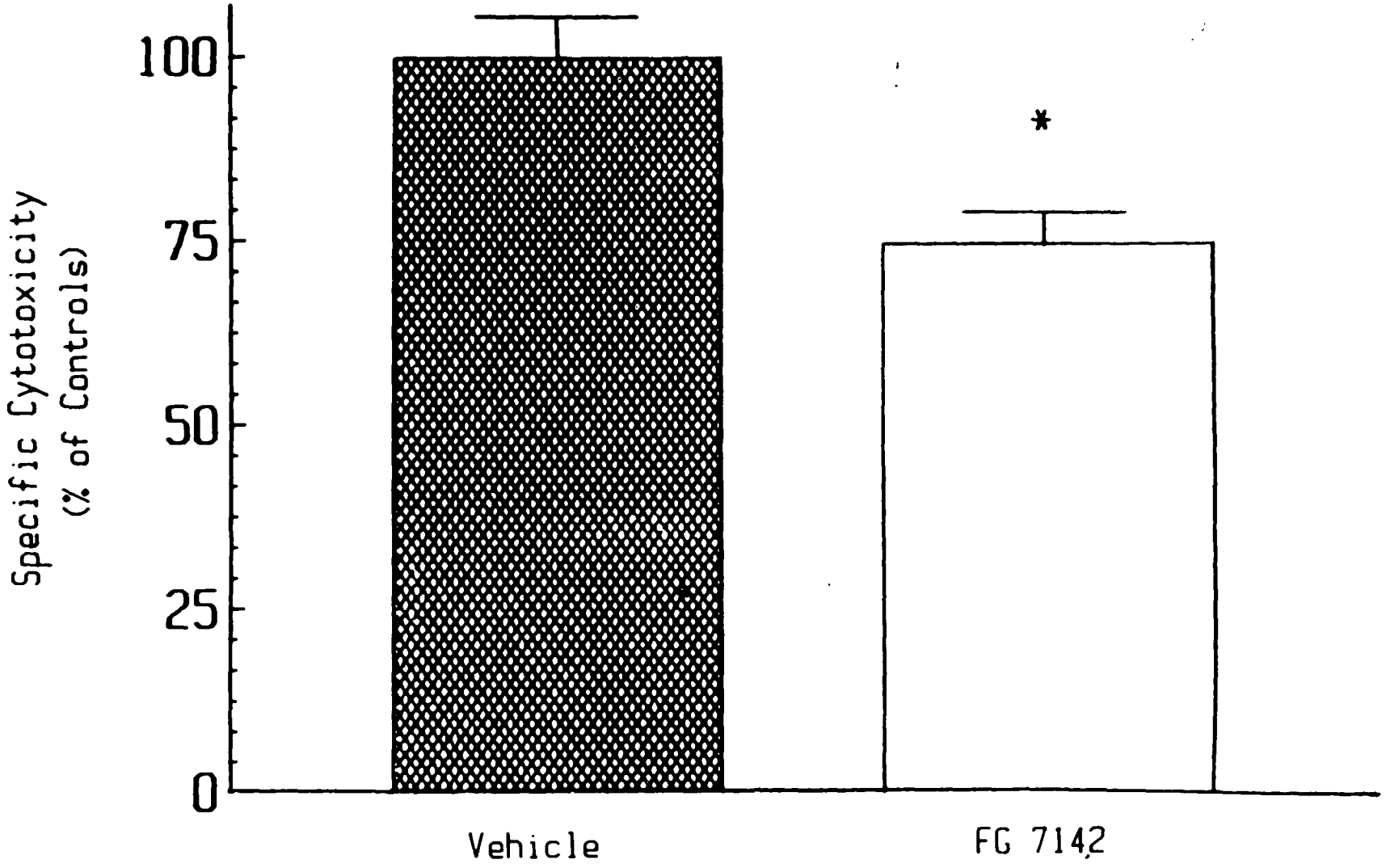
Specific Cytotoxicity
(% of Controls)
100
75
50
25
0
*
Vehicle
FG 7142

Figure. 5

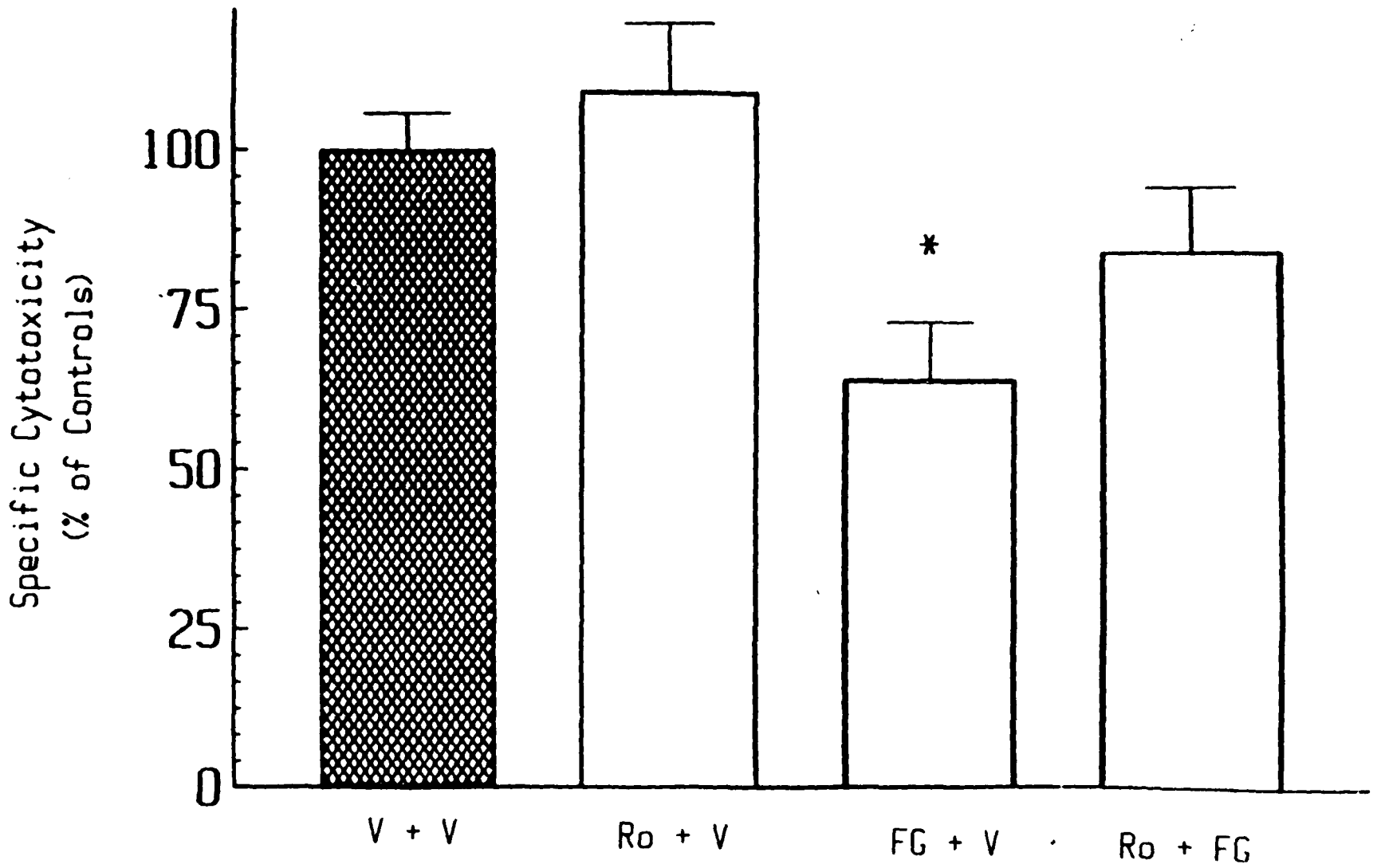
Specific Cytotoxicity
(% of Controls)
100
75
50
25
0
*
V + V
Ro + V
FG + V
Ro + FG

Figure. 6

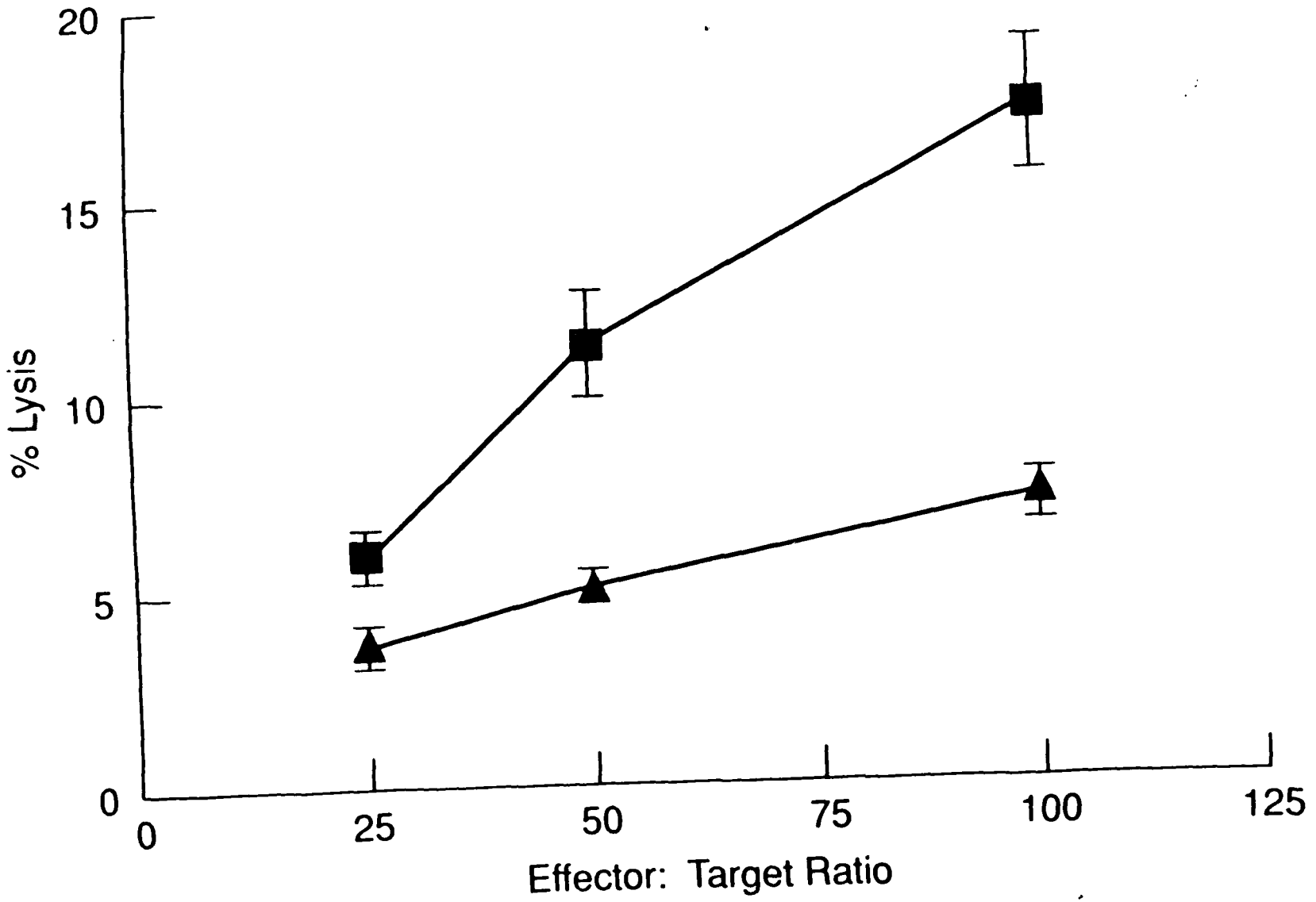

TABLE I Effects of alprazolam (ALP) on different parameters of immune function at 2, 2.5 or 24 hours after administration to male B10.BR mice.

Treatment	CTL (%lysis)	MLR (cpm)	Conc A (cpm)	PHA (cpm)	LPS (cpm)
2 HOURS					
CONTROL	55±2[4]	43661±3496	40980±5423	9286±1493	4958±328
ALP. 0.5[3]	37±5[2]	28190±1872[2]	27884±3363	5288± 993[2]	3972±113
ALP. 1.0	28±8[2]	23804±1327[2]	22837±6000	6984± 718[1]	4080±442
2.5 HOURS					
CONTROL	62±2	41502±2034	50926±6960	13885±1683	75381±6757
ALP. 1.0	40±5[2]	27969±4026[2]	61251±6219	12724±1782	71456±3938
24 HOURS					
CONTROL	45±3	68625±8090	46350±2346	15465±2120	65880±6977
ALP. 1.0	51±4	66351±4856	43218±1230	12223±1155	62217±3579

1) $p<0.05$
2) $p<0.01$
3) mg/kg
4) sem

Conc-A=concanavalin-A 0.1U/culture; PHA=phytohemagglutinin 2.5U/culture; LPS=lipopolysaccharide 10U/culture; n=5 for each group.

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Behavioral Immunology Program

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INVESTIGATORS

Dr. Itamar B. Abrass
Department of Medicine
University of Washington
Harborview Medical Center
Seattle, WA 98104

Dr. Prince K. Arora
NIDDK, Bldg. 8, Rm. 111
National Institutes of Health
Bethesda, MD 20892

Dr. Andrew S. Baum
Department of Medical Psychology
Uniformed Services University
of Health Sciences, B3050
4301 Jones Bridge Road
Bethesda, MD 20814-4799

Dr. Charles A. Bowles
Merrifield Research Lab, Inc.
P.O. Box 2362
Merrifield, VA 22116-2362

Dr. Karen Bulloch
Helicon Foundation
4622 Sante Fe Street
San Diego, CA 92109

Dr. Michael D. Cahalan
Department of Physiology and Biophysics
University of California, Irving
Irvine, CA 92717

Dr. Donald A. Chambers
Health Sciences Center
University of Illinois at Chicago
P.O. Box 6998
Chicago, IL 60680

Dr. Christopher L. Coe
Department of Psychology
Harlow Primate Laboratory
University of Wisconsin
Madison, IL 53715

Dr. Sheldon Cohen
Department of Psychology
Carnegie-Mellon University
Pittsburgh, PA 15213

Dr. Walla L. Dempsey
Dept. of Microbiology and
Immunology
The Medical College of
Pennsylvania
3300 Henry Avenue
Philadelphia, PA 19129

Dr. David L. Felten
Department of Anatomy
University of Rochester
School of Medicine
601 Elmwood Avenue
Rochester, NY 14642

Dr. John F. Hansbrough
Department of Surgery
UCSD Medical Center
225 Dickinson Street
San Diego, CA 92103

Dr. Robert L. Hunter
Department of Pathology
Emory Univ. School of
Medicine
WMB 760
Atlanta, GA 30322

Dr. Terry C. Johnson
Division of Biology
Ackert Hall
Kansas State University
Manhattan, KS 66506

Dr. Sandra Levy
University of Pittsburgh
School of Medicine
3811 O'Hara Street
Pittsburgh, PA 15213

Dr. Lester Luborsky
Department of Psychiatry
308 Piersol Building/G1
University of Pennsylvania Hospital
Philadelphia, PA 19104

Dr. Steven F. Maier
Department of Psychology
University of Colorado
Campus Box 345
Boulder, CO 80309

Dr. Diana S. Malcolm
Department of Surgery, USUHS
Uniformed Services University
of Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799

Dr. Michael H. Melner
Department of Reproductive Biology
Oregon Regional Primate Center
505 N.W. 185th Avenue
Beaverton, OR 97006

Dr. Vera B. Morhenn
Department of Dermatology
Stanford University Medical School
Stanford, CA 94305

Dr. Jose R. Perez-Polo
Gail Borden Bldg., Rm. 436
University of Texas Medical Branch
Galveston, TX 77550-2777

Dr. Howard R. Petty
Department of Biological Sciences
Wayne State University
Detroit, MI 48202

Dr. Bruce S. Rabin
Clinical Immunopathology
Childrens Hospital
University of Pittsburgh School of
Medicine
Pittsburgh, PA 15213

Dr. Seymour Reichlin
Director, Clinical Study Unit
New England Medical Center Hospitals, Inc.
171 Harrison Avenue
Boston, MA 02111

Dr. Eric M. Smith
Department of Psychiatry
University of Texas
Medical Branch
Galveston, TX 77550

Dr. Ross R. Vickers, Jr.
Naval Health Research Ctr.
Bldg. 346
P.O. Box 85122
San Diego, CA 92138

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ADMINISTRATORS

Dr. Jeannine A. Majde, Code 1141SB (2 copies)
Scientific Officer, Immunology Program
Office of Naval Research
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(address varies - obtain from business office)

Program Manager
Biological/Human Factors Division
Office of Naval Research, Code 125
800 N. Quincy Street
Arlington, VA 22217-5000

Program Manager
Support Technology Directorate
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800 N. Quincy Street
Arlington, VA 22217-5000

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Naval Medical Research Institute
National Naval Medical Center
Bethesda, MD 20814

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